

**REMARKS****A. Preliminary Remarks**

Claims 1-5, 10-13 and 16 are pending in the application. Applicants acknowledge that the sole outstanding rejection of claims 1-5, 10-13 and 16 under 35 U.S.C. § 103(a) over Advani, Int. J. Oncol. Rad. Biol. Phys. (1997) (hereinafter, the “Advani abstract”) in view of Carroll, et al., Ann. Surg. 224:323-330 (1996) (hereinafter, “Carroll”) has been maintained in the outstanding Office Action.

**B. The rejection of claims 1-5, 10-13 and 16 as obvious under 35 U.S.C. § 103(a) over Advani (1997) in view of Carroll should be withdrawn**

The Examiner maintained the rejection of all pending claims under 35 U.S.C. § 103(a) over the Advani abstract in view of Carroll. In supporting remarks, the Examiner acknowledged that Advani (1997) “does not explicitly teach that the attenuated HSV virus [R7020] could be used to treat a non-CNS tumor in vivo.” Office Action at page 3. Further, the Examiner acknowledged that Advani does not teach “the particular amount of the HSV which would be a therapeutically effective amount for reducing tumor mass.” *Id.* The Examiner continues to assert that “Carroll teaches treatment of non-CNS tumor using an attenuated HSV (hrR3). Specifically, Carroll teaches a method for treating colon carcinoma liver metastasis by administering an attenuated HSV directly to the tumor (e.g., see abstract).” *Id.* at 4. The Examiner concludes that “[o]ne of ordinary skill in the art would have been motivated to modify the method of Advani to treat a non-CNS cancer because Carroll teaches that attenuated HSVs can be used to treat non-CNS-type tumors.” Office Action at page 4. In response, Applicants disagree with the Examiner’s position.

Applicants respectfully submit that (1) the Advani abstract does not expressly or inherently disclose, or suggest, the reduction of any tumor mass; (2) the Advani abstract does not disclose or suggest that administration to a patient of HSV R7020, or any other HSV modified in accordance with the claims, would be safe; and (3) the disclosures of the Advani abstract and Carroll cannot properly be combined on the basis that each reference discloses an attenuated HSV when the mechanisms of attenuation for these HSVs are scientifically unrelated.

Applicants maintain that the Advani abstract does not disclose or suggest that HSV R7020, the sole HSV disclosed in that reference that conforms to the HSV of the pending

claims, reduces the mass of any tumor. Beyond failing to disclose or suggest the use of any HSV to treat a non-CNS tumor, the Advani abstract fails to disclose or suggest the use of any HSV to reduce a glioma tumor mass. In the attached declaration under 37 C.F.R. § 1.132, Dr. Roizman notes that the Advani abstract is completely silent on the issue of tumor mass reduction. Roizman declaration, paragraph 6. Therefore, the Advani abstract does not expressly disclose that HSV R7020 reduces any tumor mass.

Applicants submit that the Advani abstract also fails to inherently disclose that HSV R7020, or any HSV defined by the pending claims, reduces any tumor mass. “In relying upon the theory of inherency, the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.” M.P.E.P. § 2112 (IV), quoting *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Interf. 1990) (emphasis in original). In the present case, the Advani abstract discloses data relating to HSV R7020 for up to 7 days post-infection. In contrast, the specification discloses that it took 13 days after infection to begin to see SQ 20b tumor mass reduction (*see* Roizman declaration at paragraphs 5 and 6). Thus, the Examiner has not provided evidence establishing that the experimental results disclosed in the Advani abstract inherently disclose the reduction of a tumor mass attributable to HSV R7020.

The Examiner relied on the following statement in the Advani abstract as a basis for concluding that the abstract disclosed a method of using HSV R7020 to reduce a tumor mass. “Herein we demonstrate radiation enhanced viral replication as one of the interactive effects of combining IR and attenuated HSV in treating glioma xenografts and a potential therapeutic motif in the treatment of gliomas.” Office Action at page 3. The recitation of a “treatment” does not establish that a tumor mass reduction necessarily flowed from Advani’s disclosure of the administration of HSV R7020 to a xenograft-bearing mouse. The Roizman declaration, at paragraph 7, establishes that tumor treatments could either result in tumor stasis limited to simply halting tumor growth, or they could result in tumor regression, i.e., a reduction in tumor mass. Attached to the Roizman declaration as Exhibit D is U.S. Patent No. 5,342,947, which Dr. Roizman cites (paragraph 7) as evidence that tumor stasis treatment was known to halt tumor growth, but did not involve tumor mass reduction.

In addition, those of ordinary skill in the art would understand that tumor treatments resulting in a reduction in tumor mass must provide sufficient virus to generate a rate of

tumor cell death that exceeded the rate of tumor cell growth. As noted in the Roizman declaration at paragraph 10, one of ordinary skill in the art could not have concluded that the single disclosed dose of  $2 \times 10^7$  pfu HSV R7020 would necessarily lead to tumor mass reduction when the Advani abstract did not even precisely define that tumor mass or the quantity of tumor cells found in the tumor. Rather, the Advani abstract disclosed that tumors were “ $>200 \text{ mm}^3$ ,” or greater than  $200 \text{ mm}^3$ . Without knowing how many tumor cells were growing, one of skill could not have concluded that  $2 \times 10^7$  pfu HSV R7020 would result in a rate of tumor cell death that exceeded the rate of tumor cell growth, thereby leading to tumor mass reduction. The Examiner recognized this fact in remarks found at pages 17-18 of the Office Action mailed October 11, 2002 in this matter: “Advani (1997 and 1998) does not disclose that the rate of killing is faster than the rate of growth, which is required to result in the reduction of tumor mass.” Consistent with that view, in the outstanding Office Action the Examiner stated that Advani does not teach “the particular amount of the HSV which would be therapeutically effective amount for reducing tumor mass.” Office Action at page 3.

For all of the foregoing reasons, the Advani abstract did not disclose, expressly or inherently, the use of HSV R7020 in a tumor treatment method that led to a reduction in tumor mass.

The Advani abstract also does not disclose, expressly or inherently, a therapeutically effective dose of an HSV, as recited in the pending claims. A therapeutically effective dose, as would be understood by one of ordinary skill in the art, is a dose that is both efficacious and safe. The preceding discussion established that the Advani abstract did not provide evidence that HSV R7020 was efficacious in reducing a glioma tumor mass. The Advani abstract also failed to disclose, expressly or inherently, that the administered dose of  $2 \times 10^7$  pfu HSV R7020 would be safe insofar as it would not exhibit unacceptable toxicity towards healthy cells of the treated subject. The Advani abstract confined its disclosure to an examination of tumor tissue. The Advani abstract provides no disclosure of any effect, or absence of an effect, of HSV R7020 on any non-tumor tissue. Accordingly, one of ordinary skill in the art would not have the view that the Advani abstract disclosure of the administration of  $2 \times 10^7$  pfu HSV R7020 is safe and, thus, that such a dose is a therapeutically effective amount.

In rejecting the claims as obvious under 35 U.S.C. § 103(a), the Examiner relied on the Advani abstract in combination with Carroll. Carroll, however, does not remedy the

defects in the Advani abstract, such as the failure to disclose or suggest that an HSV according to the pending claims would be useful in reducing a tumor mass or that such an HSV would be sufficiently safe to yield a dose that would be a therapeutically effective amount. The Examiner relied on Carroll as disclosing the use of an attenuated HSV (i.e., HSV hrR3) to treat a non-CNS tumor. Beyond failing to remedy either defect in the Advani abstract noted above, Carroll cannot be properly combined with the Advani abstract in support of the rejection.

The Advani abstract discloses HSV R7020 as an HSV in accordance with the claims. The sole virus disclosed in Carroll, HSV hrR3, is not an HSV in accordance with the claims, and the Examiner has not asserted otherwise. The Examiner has effectively asserted that any attenuated HSV can be substituted for any other attenuated HSV, and Applicants disagree with that position. As noted in the Roizman declaration at paragraphs 18-20, the mechanisms of attenuation of Advani's HSV R7020 and Carroll's HSV hrR3 are completely different. Advani's HSV R7020 is a multi-mutated virus that includes the loss of one of two copies of the  $\gamma_134.5$  gene. Roizman declaration, paragraph 18. In contrast, HSV hrR3 has a mutation in the  $U_L39$  gene leading to loss of viral ribonucleotide reductase. Roizman declaration, paragraph 19. As explained by Dr. Roizman in paragraphs 20-22 of the declaration, the mechanisms of attenuation for HSV R7020 (Advani) and HSV hrR3 (Carroll) are distinct. The Roizman declaration states that, for these reasons, one of ordinary skill in the art would not look to Carroll as a guide for modifying any method disclosed in the Advani abstract. Accordingly, there is no proper reason for combining the disclosures of the Advani abstract and Carroll.


For all of the foregoing reasons, Applicants submit that the rejection of each of claims 1-5, 10-13 and 16 as obvious under 35 U.S.C. § 103(a) over the Advani abstract in view of Carroll has been overcome and the rejection may properly be withdrawn.

**C. Conclusion**

For all of the foregoing reasons, Applicants submit that all outstanding rejections and objections have been overcome and claims 1-5, 10-13, and 16 are in condition for allowance. An early notice thereof is respectfully solicited.

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Respectfully submitted,

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